

### **REMARKS**

Claim 88 is newly added herein. Claims 34-41, and 47 have been amended herein. Claims 1, 44-46, and 48-50 have been canceled herein. Such cancellation is without prejudice on the merits to further prosecution of these claims in one or more continuing applications.

Claims 34-43, 47, and 51-57 are currently active in the case. (Claims 58-87 are currently withdrawn from consideration due to the prior restriction requirement.)

Favorable reconsideration is respectfully requested

The following comments address the issue presented in the Office Action dated September 17, 2003 in the order of their appearance.

#### **Objection to Claim 47:**

This objection has been overcome by amendment to Claim 47 in accordance with the Examiner's recommendation. As amended, Claim 47 now depends from Claim 43.

#### **Rejection of Claims 1, 34, 35, 41, 42, 43, and 49 Under 35 USC §102(b) Over Steers et al., U.S. Patent No. 5,698,549:**

As applied to Claims 1 and 49, this rejection has been rendered moot by cancellation of the claims.

As applied to Claims 34, 35, and 41-43, this rejection is believed to have been overcome by appropriate amendment to the claims. Specifically, all of Claims 34, 35, and 41-43 now require the presence of calcitonin, a compound that is not disclosed anywhere within the Steers et al. patent.

Specifically, Claims 34 and 35 now depend from new Claim 88. Note that Claim 88 restricts the scope of now-canceled Claim 1 by requiring the presence of calcitonin as an essential feature of the composition. In Claim 88, the term "contacting" is used to indicate external application to sperm as opposed to injection. The term "consisting essentially of" is used to exclude from the scope of Claim 88 compositions containing significant amounts of other materials which might act against the specified components of

the composition or adversely affect the desired biological action of sperm. At the same time, this term is intended to include within the scope of Claim 88 compositions containing relatively minor amounts of other, non-interfering materials conventionally used in fertility treatment, *e.g.*, components found in culture media in which sperm and egg are brought together to achieve successful fertilization, and the like.

Likewise, Claim 41 as amended (and the claims dependent thereon) requires that the composition include calcitonin, angiotensin II, and a modulator or adenosine receptor activity.

In short, the Steers et al. patent is concerned with compositions for systemic use and containing calcium channel blockers. Calcitonin is not a material of this kind and **no mention of calcitonin** is made by Steers et al.

Additionally, there is a reference to inhibitors of angiotensin-converting enzyme (ACE) in column 16, line 54 of Steers et al., but no reference to the use of angiotensin itself.

Moreover, the Steers et al. patent is couched entirely in the context of a treatment for hypertension. In column 17, lines 15-18 (cited by the Office), Steers et al. refer to angiotensin II and to "angiotensin II paired with adenosine." However, this pairing is referenced in a negative light. Steers et al. state that angiotensin II paired with adenosine "increases NGF output." Note, however, that the entire purpose of the invention disclosed in Steers et al. is to **decrease** NGF output. See, for example, Steers et al., column 4, lines 51-54: "A non-invasive marker for the analysis of increased NGF in association with voiding disorders would allow for a rapid, inexpensive method of indicating a disorder." In Steers et al.'s work, increased NGF is a condition to be avoided, not courted.

Thus in no fashion do Steers et al. provide any motivation for pairing angiotensin II with adenosine. In fact, Steers et al. motivates the opposite. The cited passage at column 17, lines 15-18 of Steers et al. clearly counsels against of the use of angiotensin II paired with adenosine because it will increase the output of NGF.

Because the Steers et al. reference is completely silent with regard to a composition containing calcitonin, and also motivates against combining angiotensin II and adenosine,

Applicants submit that this rejection has been overcome. Withdrawal of the same is respectfully requested.

**Rejection of Claims 1, 40, 41, 46, and 52 Under 35 USC §102(b) Over Schmid et al.:**

As applied to Claims 1 and 46, this rejection has been rendered moot by cancellation of the claims.

As applied to Claims 40, this rejection is respectfully traversed. The Schmid et al. paper reports an essentially academic study of the effect of calcitonin on certain neurons in the rat. The effect of angiotensin II in this context is of no interest to these authors and steps are taken to exclude any direct effect of this substance in the experiments described.

The Examiner refers to "the disclosed composition" in this reference (see page R1649, upper section of column 2). However, it is by no means certain precisely what composition is meant by Schmid et al. in this part of the reference. Thus it is not clear whether Schmid injected a single composition containing calcitonin and angiotensin II or whether he used separate injections of these substances at about the same time.

That being said, the proper interpretation of the Schmid disclosure can be deduced from the following observations:

From the legend below Figure 6 of Schmid and the description in the first half of column 2 on page R1649, there is reference to the use of losartan. Losartan is a compound that Schmid et al. state "is known to abolish ANG II-induced drinking in rats (Fig 6)." It is further written that the losartan is given to the rats as a pre-treatment "30 minutes before the subcutaneous injection of calcitonin." Therefore in the legend to Figure 6, the reference to "calcitonin + losartan" **cannot** mean a combined injection of these two substances. The two compounds were clearly given separately, with a 30-minute time span separation.

Thus, the abbreviated legend notation "ANG II + calcitonin" does not indicate that the two compounds were given in a combined pharmaceutical composition. Rather, the two substances were given individually, separated by a 30-minute span. (Note also that Schmid's use of the term "together" is wholly ambiguous.)

What is beyond doubt, however, is that Schmid et al. are not recommending, teaching, or suggesting to the reader to use a functional combination of calcitonin and angiotensin II for any purpose whatsoever. Schmid et al. fail to ascribe ANY pharmaceutical functionality or use to a combination of calcitonin and angiotensin II. In short, contrary to the assertion made by the Office, Schmid et al. do not disclose a pharmaceutical composition because, even assuming that Schmid et al. administered calcitonin and angiotensin II together (which they did not), Schmid et al. have no purpose whatsoever in performing the injection. No condition is being treated. No utility is ascribed.

The primary concern of Schmid et al. is to isolate the effect of calcitonin on neurons (as contrasted to the effect of angiotensin II on these same neurons). Hence, their use of losartan as an inhibitor of the angiotensin II. The incontrovertible fact remains that Schmid et al. exposed their rats to calcitonin and an inhibited amount of angiotensin II; the losartan (an angiotensin II inhibitor) was administered prior to the angiotensin II. Thus, the Schmid et al. paper is of no possible relevance to the present invention because the pre-addition of the inhibitor (losartan) prevents the angiotensin II from exerting any biological effect in the system described.

Schmid et al. therefore do not disclose a composition in which both or all of the defined components are biologically functional. Hence the Schmid composition does not meet the terms of Claim 40 as amended or Claim 88 as submitted herein.

Furthermore, for the reasons expressed above, it is inconceivable that this citation would point the skilled person toward a composition of matter in which calcitonin is combined with angiotensin II or another of the defined components, in a fully functional manner, to increase the capacitation of sperm in the manner defined in the amended claims.

As applied to Claims 41 and 52, this rejection is submitted to have been overcome by appropriate amendment to Claim 41. Specifically, as amended, Claim 41 positively requires the presence of calcitonin, angiotensin II, and a modulator or adenosine receptor

activity. The Schmid et al. reference simply does not disclose such a composition. Therefore, the Schmid et al. reference does not anticipate either of Claims 41 or 52.

For the reasons given above, Applicants submit that the rejection of Claims 1, 40, 41, 46, and 52 under 35 USC §102(b) over Schmid et al. is no longer tenable. Withdrawal of the same is respectfully requested.

**Rejection of Claims 1, 34, 35, 40-43, 45, 52, and 53 Under 35 USC §102(b) Over Skelnick, U.S. Patent No. 6,153,582:**

As applied to Claims 1 and 45, this rejection has been rendered moot by cancellation of the claims.

As applied to Claims 34, 35, 40-43, 52, and 53, this rejection is believed to have been overcome, in part, by appropriate amendment to the claims, and is, in part, respectfully traversed.

The Skelnick patent is concerned with ophthalmic treatments designed to preserve and enhance eye tissues. Thus, this patent provides compositions for that purpose. The compositions described by Skelnick are highly complex mixtures of 16 or more diverse types of ingredient, each type embracing numerous possible alternative materials. The total number of possible combinations of materials envisaged by this disclosure is enormous. Although calcitonin and adenosine are given as examples of two of the possible ingredients, this particular combination represents but one selection from a vast number of combinations containing other materials which are essential for the envisaged optical application. A combination consisting essentially of calcitonin and adenosine (as in Claim 88 and the claims dependent thereon) is certainly not taught by Skelnick.

The likelihood that the great majority of the combinations required by Skelnick would have some deleterious effect on sperm is very considerable. For example, many of the combinations would produce highly viscous solutions which would reduce sperm motility. Many of these components listed by Skelnick are known not to support capacitation and fertilization. Some have negative effects on sperm, or cause sperm to over-capacitate, or are toxic to sperm. The awesome number of permutations comprised in

the Skelnik lists would make it impracticable to demonstrate these facts by experimental tests. Such experimentation would be undue in the extreme.

The Examiner is requested to take account of these considerations averred by the inventor of the subject application. Dr. Fraser is an acknowledged expert in the science of human reproduction, as is clear from the Rule 132 Declaration filed in connection with now-allowed companion US application 09/857,131 (directed to the use of calcitonin alone). A courtesy copy of this Declaration is attached hereto for the Examiner's convenience.

In light of the amendment to the claims, and the inapposite disclosure of the Skelnik patent, it is respectfully submitted that the rejection of Claims 34, 35, 40-43, 52, and 53 under §102(b) in view of Skelnik is untenable. Withdrawal of the same is respectfully requested.

**Rejection of Claims 1 and 34-57 Over the Combination of WO 95/32725, Suzuki et al., and Fraser:**

As applied to Claims 1, 44-46, and 48-50, this rejection has been rendered moot by cancellation of the claims.

As applied to Claims 34-43, 47, and 51-57, this rejection is believed to have been overcome, in part, by appropriate amendment to the claims, and is, in part, respectfully traversed.

As noted earlier, Claim 1 has been replaced with Claim 88. Claim 88 positively requires the presence of calcitonin as an essential feature of the composition. Likewise, Claim 41 as amended (and the claims dependent thereon) positively requires that the composition include calcitonin, angiotensin II, and a modulator or adenosine receptor activity. Thus, it is respectfully submitted that this rejection has been overcome, in major part, by amendment to the claims.

This rejection is traversed, in part, because WO 95/32725 is not directed to increasing the capacitation of sperm (as alleged by the Office at page 6 of the Office Action). In fact, the term "capacitation" does not appear anywhere in the document.

This citation is directed only to improving the motility of sperm. The WO document has no bearing whatsoever on capacitation and the control of the acrosome reaction. Motility is not the same as capacitation. The WO reference is wholly and completely silent regarding capacitation.

Combining the WO document with Fraser (IDS-4) is unhelpful because Fraser does not even mention calcitonin or angiotensin. (The Office admits the same at page 6 the Office Action.) Calcitonin is a required element of all of the now-pending claims.

The Fraser paper is a review published in *Andrologia* 30:241-247: "Modulation of mammalian sperm function by fertilization promoting peptide (FPP)." In it, the inventor summarized her findings relating to FPP, including the fact that the use of "FPP + adenosine had a greater effect on uncapacitated cells than either used individually." Because Professor Fraser already knew that adenosine could stimulate adenylyl cyclase's production of cAMP, this observation allowed her to the view that FPP works on the same pathway, but via different receptors. In the section on peptide structure-function relationships, it was stated that about half of all small bioactive peptides have an amide (NH<sub>2</sub>) group attached to the carboxy-terminal end of the peptide. Removal of the amide group generally results in loss of activity. Examples of such peptides were given: corticotrophin-releasing hormone, gonadotrophin-releasing hormone, calcitonin, gastrin, and thyrotrophin releasing hormone. At the time Professor Fraser wrote this review, she had not begun to study calcitonin and so had no knowledge that it could actually work on sperm. And, critical to the present rejection, the reference makes no suggestion that it will work on sperm.

Thus, the combined teaching of the WO and Fraser references still fails to suggest using the presently claimed compositions to increase the capacitation of sperm.

The Suzuki et al. reference (IDS-2) reports that calcitonin induces capacitation of guinea pig sperm and the acrosome reaction. However, an analysis of this citation shows that the authors are confusing capacitation with the acrosome reaction. In short, Suzuki and are assuming that the acrosome reaction is an indication that capacitation has been stimulated by the addition of calcitonin.

It is apparent to the skilled person that this assumption is incorrect and that Suzuki et al. are not using the term "capacitation" in the correct sense. This reference shows that sperm treated with calcitonin undergo a spontaneous acrosome reaction following the addition of calcium. It is assumed that the acrosome reaction is an indication that capacitation has been stimulated. This assumption would be immediately seen as incorrect by the skilled person at the date on which the present invention was made. The results reported by the scanty data provided by Suzuki et al. are totally inconsistent with the findings of the present inventor, which are convincingly documented in the present application and in companion Application 09/857,131.

Further discussion of Suzuki is made difficult by the absence of detail as to concentrations of materials used and lack of information regarding the controls used. The authors incubated sperm for 1 hour in calcium-deficient medium with or without added calmodulin or calcitonin (no concentrations given).

They then added calcium and evaluated sperm after a further 20 minutes. No results are given for % acrosome-reacted control sperm. Thus it is impossible to evaluate the data obtained in the groups incubated with calmodulin and calcitonin.

The authors are using the term "capacitation" as a synonym for the acrosome reaction, but this is incorrect, as pointed out above.

It is not possible to interpret the results obtained in the "hamster test" because no details are given.

It is respectfully submitted that the skilled person would not give credence to the Suzuki et al. reference due to the paucity of details provided by the document.

Thus, taken together, these three references do not render obvious the present claims because: 1) the WO reference has nothing whatsoever to do with capacitation of sperm; 2) the Fraser reference fails entirely even to mention calcitonin or angiotensin II; and 3) the Suzuki et al. reference fails entirely even to enable a person of ordinary skill in the art even to repeat the experiments described within the reference itself. Taken in total, or in any sub-combination, these three references combined fail to provide a reasonable likelihood of success in arriving at the present invention. The combination neither teaches

the invention as claimed, nor suggests it, nor motivates a person of skill to arrive at the present invention.

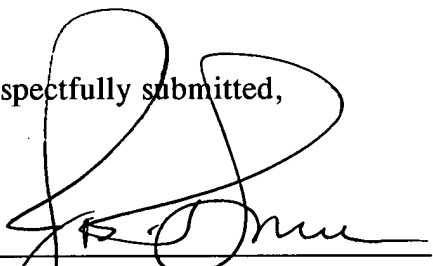
For the above reasons the assertion by the Office that these three references together render obvious the claimed combination is untenable. The Examiner is referred to the section of the present application from page 3, line 25, to page 4, line 6, which shows that the augmentation effect is by no means an easy and predictable deduction from what is known about these hormones.

Withdrawal of this rejection is therefore respectfully requested.

### CONCLUSION

Applicants submit that the application is now in condition for allowance. Early notification of such action is earnestly solicited.

Respectfully submitted,

  
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